Full research paper

European Journal of Preventive Cardiology

ESC European Society of Cardiology

European Journal of Preventive Cardiology
2020, Vol. 27(3) 311–320

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DOI: 10.1177/2047487319890973
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Screening young athletes for diseases at risk of sudden cardiac death: role of stress testing for ventricular arrhythmias

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Abstract

Aims: The athletic preparticipation evaluation (PPE) protocol proposed by the European Society of Cardiology includes history, physical examination and resting electrocardiogram (ECG). The aim of this study was to assess the results of adding constant-load ECG stress testing (EST) to the protocol for the evaluation of ventricular arrhythmias (VA) inducibility.

Methods: We evaluated a consecutive cohort of young athletes with history, physical examination, resting ECG and EST. Athletes with VA induced by EST underwent 24-hour 12-lead Holter monitoring and echocardiography. Cardiac magnetic resonance (CMR) was reserved for those with frequent, repetitive or exercise-worsened VA, and for athletes with echocardiographic abnormalities.

Results: Of 10,985 athletes (median age 15 years, 66% males), 451 (4.1%) had an abnormal history, physical examination or resting ECG and 31 (0.28%) were diagnosed with a cardiac disease and were at risk of sudden cardiac death. Among the remaining 10,534 athletes, VA at EST occurred in 524 (5.0%) and a previously missed at-risk condition was identified in 23 (0.22%); the most common ($N = 10$) was an echocardiographically silent non-ischaemic left-ventricular fibrosis evidenced by CMR. The addition of EST increased the diagnostic yield of PPE by 75% (from 0.28% to 0.49%) and decreased the positive predictive value by 20% (from 6.9% to 5.5%). During a 32 ± 21 months follow-up, no cardiac arrests occurred among either eligible athletes or non-eligible athletes with cardiovascular disease.

Conclusions: The addition of exercise testing for the evaluation of VA inducibility to history, physical examination and ECG resulted in an increase of the diagnostic yield of PPE at the expense of an increase in false-positive findings.

Keywords

Cardiac magnetic resonance, late enhancement, premature ventricular beats, sports cardiology, sudden cardiac death

Received 14 October 2019; accepted 6 November 2019

Introduction

Preparticipation evaluation (PPE) offers the potential to prevent sudden cardiac death (SCD) in young athletes by early identification of cardiac diseases at risk of malignant ventricular arrhythmias (VA).[1] The protocol of PPE proposed by the European Society of Cardiology includes history, physical examination and baseline electrocardiogram (ECG). Further examinations are reserved to individuals with abnormalities at first-line evaluation.[2] Although this protocol allows for the identification of ECG-detectable cardiovascular disorders including overt cardiomyopathies, cardiac ion channel diseases and ventricular pre-excitation syndromes, it lacks sensitivity for segmental cardiomyopathies, acute myocarditis, non-ischaemic left-ventricular

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(LV) myocardial fibrosis and coronary artery disease, either congenital or acquired.[3] Moreover, standard echocardiographic examination demonstrated little additional value for the identification of these concealed conditions.[4–7]

According to the 1982 Italian law, the PPE protocol includes a constant-load ECG stress test (EST; modified Montoye step test), in addition to history, physical examination and resting ECG. Originally, the aim of EST was to assess the cardiological fitness for sports activity by evaluating the 'immediate recovery index' (IRI), based on the heart rate from the third to the fifth minute of recovery.[8] More recently, the EST has been upgraded and is currently performed by many sports medicine centres using a bicycle or treadmill and under continuous ECG monitoring. This has allowed the occurrence, morphology and complexity of VA to be assessed during the EST, which may be the only phenotypic manifestation of an underlying disease in athletes with negative history, unremarkable physical examination and normal resting ECG. However, the effect of VA induced by EST on the diagnostic yield and the positive predictive value of PPE remains to be established.

The aim of this study was to assess the results of adding an EST for the evaluation of VA to the traditional PPE protocol consisting of history, physical examination and resting ECG.

Methods

The study included a consecutive series of competitive non-professional athletes from 12 to 35 years old undergoing annual PPE between 2013 and 2018 at the Center for Sports Medicine, Treviso, Italy. The study was prospective, complied with the Declaration of Helsinki and was approved by the ethical committee of the province of Treviso (#643). Consent from athletes was not required because data were completely anonymised.

Screening protocol

The protocol for cardiovascular evaluation to be eligible to compete in a sport activity is established by Italian law.[8] According to this protocol, cardiovascular evaluation includes history, physical examination with blood pressure measurement, resting 12-lead ECG and EST. Classification of resting ECG abnormalities was based on the 2013 international recommendations for ECG interpretation in athletes.[9] Further examinations such as 24-hour ambulatory ECG monitoring and echocardiography were required for those athletes with abnormal findings at first-line evaluation. At the end of the diagnostic work-up, a sports eligibility decision was taken based on the indications of the 'cardiovascular protocols for competitive sport eligibility' by the Italian Society of Sports Cardiology.

ECG stress testing: Protocols and evaluation of ventricular arrhythmias

All athletes underwent EST that was modified compared with the original Montoye step test with post-exercise ECG recording prescribed by the law. The test was upgraded with continuous 12-lead ECG monitoring throughout the test not only for measurement of IRI, but also to evaluate the occurrence, morphology and complexity of exercise-induced VA. The protocol consisted of a bicycle EST with a constant-load (2–3 W/kg according to gender) for 3 minutes or until more than 85% of the maximal theoretical heart rate (220 – age) was achieved. Monitoring continued for at least 3 minutes post-exercise.

Additional work-up of athletes with premature ventricular beats (PVBs) at EST included echocardiography and 24-hour 12-lead ambulatory ECG monitoring. The echocardiographic examination was performed according to a previously reported protocol.[10] The 24-hour ECG monitoring consisted of a 12-lead system configuration (H12+, Mortara Instruments Inc.). Athletes were asked to perform a training session of at least 30–60 minutes during the ambulatory ECG recording. Every single ectopic beat, pause or artefact and all families of normal beats were confirmed manually. Recordings with more than two hours of artefacts or missing signals were considered inadequate and repeated. Morphology of VA, which was evaluated if more than 10 PVBs were present, was classified as left-bundle-branch-block-like (LBBB) if the ectopic QRS was predominantly negative in lead V1, right-bundle-branch-block-like (RBBB) if the ectopic QRS was predominantly positive or isodiphasic in lead V1. PVBs with a LBBB/inferior axis (positive QRS in aVF and negative QRS in V1 and aVL) configuration were considered of ventricular outflow tract origin; PVBs with a QRS duration of 130 ms or less resembling a typical RBBB/left or right axis deviation were considered of fascicular origin.[11,12] PVBs with two or more morphologies that accounted for 10% or more of all PVBs were classified as multifocal.

Cardiac magnetic resonance

Contrast-enhanced cardiac magnetic resonance (CMR) was reserved for athletes showing one or more of the following criteria: 1. non-sustained ventricular tachycardia ($\geq$3 consecutive PVBs) at EST or 24-hours ECG monitoring; 2. VA that increased in frequency/complexity with increasing heart rate during

EST; 3. frequent (>500/day) PVBs at ambulatory ECG monitoring, excluding isolated and monomorphic PVBs with a morphology suggestive of outflow tract or fascicular origin; and 4. echocardiographic abnormalities suggestive of cardiomyopathy. The CMR protocol has been reported in detail previously.[10] Isolated junctional late gadolinium enhancement (LGE; i.e. at the insertion points of the right-ventricular (RV) free wall to the interventricular septum) was not considered abnormal as it is a common finding in athletes. All CMR data were reviewed by two experts (AC, MDL) who were blinded to clinical data, in case of disagreement a third expert was consulted (MPM).

Statistical analysis

Continuous and categorical variables were expressed as median (with 25th–75th percentiles) and *n* (%), respectively. A 95% confidence interval (CI) was calculated based on the binomial distribution. Categorical variables were compared using the chi-squared or Fisher's exact test, as appropriate. Continuous data were compared using the Mann–Whitney *U* test because normality could not be assumed for any variable. A *p* value <0.05 was considered statistically significant. The positive predictive value of two different PPE protocols (with and without EST) was calculated as true positives/true positives + false positives. Data were analysed with SPSS® version 23 (IBM®). Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Padova.

Results

History, physical examination and baseline ECG

During the 5-year study period, 10,985 non-professional competitive athletes (66% males, median age 15 [13–18] years, 97% White) underwent PPE. Of those, 451 (4.1%, 95% CI 3.7%–4.5%) showed positive medical history, pathological physical examination or abnormal baseline ECG. Additional investigation led to the identification of a cardiac disease at risk of SCD in 31 (0.29%, 95% CI 0.20%–0.42%), including long QT-syndrome ($N=9$), hypertrophic cardiomyopathy ($N=5$), arrhythmogenic cardiomyopathy ($N=4$), dilated cardiomyopathy ($N=4$), at-risk ventricular preexcitation ($N=3$), Marfan syndrome with aortic dilatation ($N=2$), myocarditis ($N=2$), LV non-compaction ($N=1$) and Brugada syndrome ($N=1$).

Of the remaining 10,534 athletes with a normal history, physical examination and baseline ECG, 524 (5.0%, 95% CI 4.6%–5.4%) showed PVBs at EST including 73 (14%) with couplets or non-sustained ventricular tachycardia (Table 1). Arrhythmias were observed before exercise in 126 (24%) athletes, during the initial phase of the test (first and second minute) in 204 (39%), at peak of exercise (i.e. during the third minute) in 88 (17%) and during the post-exercise phase in 253 (48%). In 27 (5%) athletes, VA occurred only at peak of exercise.

Table 1. Characteristics of patients with normal history, physical examination and ECG according to the presence of ventricular arrhythmias at stress testing.

	Arrhythmias present $N=10{,}010$	Arrhythmias absent $N=524$	*p*
Age (years)	15 [13–18]	15 [14–17]	0.64
Males	6724 (67%)	373 (71%)	0.06
Sports disciplines			
Soccer	2301 (23%)	122 (23%)	0.88
Volleyball	1782 (18%)	79 (15%)	0.11
Basketball	1324 (13%)	71 (14%)	0.82
Rugby	881 (9%)	59 (11%)	0.05
Athletics	771 (8%)	15 (3%)	<0.001
Skating	641 (6%)	23 (4%)	0.05
Swimming	502 (5%)	25 (5%)	0.80
Gymnastics	290 (3%)	12 (2%)	0.42
Martial arts	287 (3%)	21 (4%)	0.13
Tennis	230 (2%)	10 (2%)	0.56
Dancing	224 (2%)	15 (3%)	0.35
Other (<2%)	777 (8%)	72 (14%)	<0.001

Data are presented as *N* (%) or median [25%–75% percentiles].

Additional tests in athletes with VA

The 12-lead 24-hour ambulatory ECG monitoring findings among athletes with VA are shown in Table 2. A total of 303 (58%) athletes showed less than 10 PVBs while 107 (21%) more than 500 PVBs. Couplets or non-sustained ventricular tachycardia were recorded in 132 (25%) athletes. Among the 221 athletes with 10 PVBs or more, 164 (75%) showed monomorphic PVBs (fascicular, $N=2$; LBBB, $N=110$; and RBBB, $N=52$) while 57 (25%) exhibited multifocal VA.

Echocardiography was distinctively abnormal in 12 (2.3%) athletes. A cardiac disease at risk of SCD was diagnosed in five athletes (1.0%), including dilated cardiomyopathy ($N=1$) and congenital heart disease ($N=4$, including origin of the left coronary artery from the right coronary sinus in one, interatrial septal defect with RV dilation in one and patent ductus arteriosus with significant shunt in two; Figure 1). Regional ventricular wall motion abnormalities in the absence of other disease features were revealed in seven athletes

Table 2. 24-hour ambulatory ECG monitoring findings among the 524 athletes with ventricular arrhythmias.

	$N = 524$
Mean HR (bpm)	81 [74–87]
Min HR (bpm)	46 [42–57]
Max HR (bpm)	189 [180–203]
Max/MaxT HR (%)	92 [88–99]
PVBs count	9 [1–210]
PVBs >500/24 hours	107 (21%)
Arrhythmia grading	
Isolated PVBs only	390 (75%)
≥1 couplet	94 (18%)
≥1 NSVT	38 (7%)
Prevalent VA morphology*	
Infundibular	41 (8%)
Fascicular	2 (0.4%)
LBBB and inter./sup. axis	69 (13%)
RBBB and QRS>130 ms	52 (10%)
Multifocal	57 (11%)
VA during training session	83 (38%)

Data are presented as *N* (%) or median [25%–75% percentiles].
bpm: beats per minute; HR: heart rate; LBBB: left-bundle-branch-block; Max/MaxT HR: ratio between maximal heart rate recorded during ambulatory ECG monitoring and theoretical maximal heart rate corrected for age (220 – age); NSVT: non-sustained ventricular tachycardia; PVBs: premature ventricular beats; RBBB: right-bundle-branch-block; VA: ventricular arrhythmia.
*Among athletes with at least 10 PVBs.

(of the right ventricle in five and of both ventricles in two) who were referred for CMR. In five cases the abnormalities were confirmed and found to be associated with LV LGE. Minor cardiac abnormalities were diagnosed by echocardiography in 54 (10.3%) athletes, including mitral valve prolapse with no significant mitral regurgitation in 48 and uncomplicated bicuspid aortic valve in 6.

CMR

A total of 87 out of 524 (17%) athletes with VA at EST underwent CMR. Reasons for CMR study included: non-sustained ventricular tachycardia at EST or 24-hour ECG monitoring ($N = 40$), VA that increased in frequency/complexity with increasing heart rate during exercise ($N = 57$), >500 PVBs at 24-hour ambulatory ECG monitoring with morphologies other than fascicular or infundibular ($N = 29$) and/or regional wall motion abnormalities at echocardiography ($N = 7$). Among the 87 athletes, CMR was abnormal in 18 (21%). In particular, one athlete had partial anomalous venous return, one athlete had pericardial LGE suggesting pericarditis, five athletes showed LV LGE with a non-ischaemic (i.e. subepicardial/midmyocardial stria pattern) distribution associated with regional wall motion abnormalities of the RV ($N = 3$) or both ventricles ($N = 2$), one athlete showed mitral valve prolapse with spotty LGE at the insertion point of the posterior mitral valve leaflet and 10 athletes showed isolated non-ischaemic LV LGE (multiple LGE spots in one and subepicardial/midmyocardial stria in nine involving 4–16% of the LV myocardium, median 7%). Overall, 16/18 athletes with an abnormal CMR showed LV LGE with a non-ischaemic distribution (Figure 2).

Predictors of LV late enhancement at CMR

The characteristics of athletes who underwent CMR according to the presence of LV LGE are shown in Table 3. Athletes with LV LGE demonstrated a higher prevalence of couplets/non-sustained ventricular tachycardia at EST and, at 12-lead 24-hour ECG monitoring, a higher prevalence of PVBs with a RBBB/wide QRS morphology (i.e. consistent with the LV distribution of the myocardial lesion), either in isolation or in association with PVBs with a LBBB pattern. Conversely, athletes with LV LGE showed a lower number of PVBs at 24-hour ECG monitoring than those without.

Genetic testing for catecholaminergic polymorphic ventricular tachycardia

Genetic testing for pathogenetic mutations of the ryanodine receptor or calsequestrin genes responsible for catecholaminergic polymorphic ventricular tachycardia was performed in six athletes with multifocal VA that increased in complexity during ET and negative CMR. The test results were negative in all six.

Addition of EST for VA inducibility to the preparticipation screening protocol

Overall, 23 of 10,534 (0.22%, 95% CI 0.14–0.33%) athletes with negative history, physical examination and baseline ECG received a diagnosis of a cardiac disease at risk of SCD following investigations for VA recorded during EST including idiopathic non-ischaemic LV scar ($N = 10$), arrhythmogenic cardiomyopathy ($N = 5$), congenital heart disease ($N = 5$), dilated cardiomyopathy ($N = 1$), pericarditis ($N = 1$) and mitral valve prolapse associated with myocardial fibrosis ($N = 1$). This equates to a 75% increase (from 31/10.985, 0.28% to 54/10.985, 0.49%) in the diagnostic yield of a PPE protocol including EST for VA compared with history, physical examination and resting ECG only. At the same time, the number of athletes who were

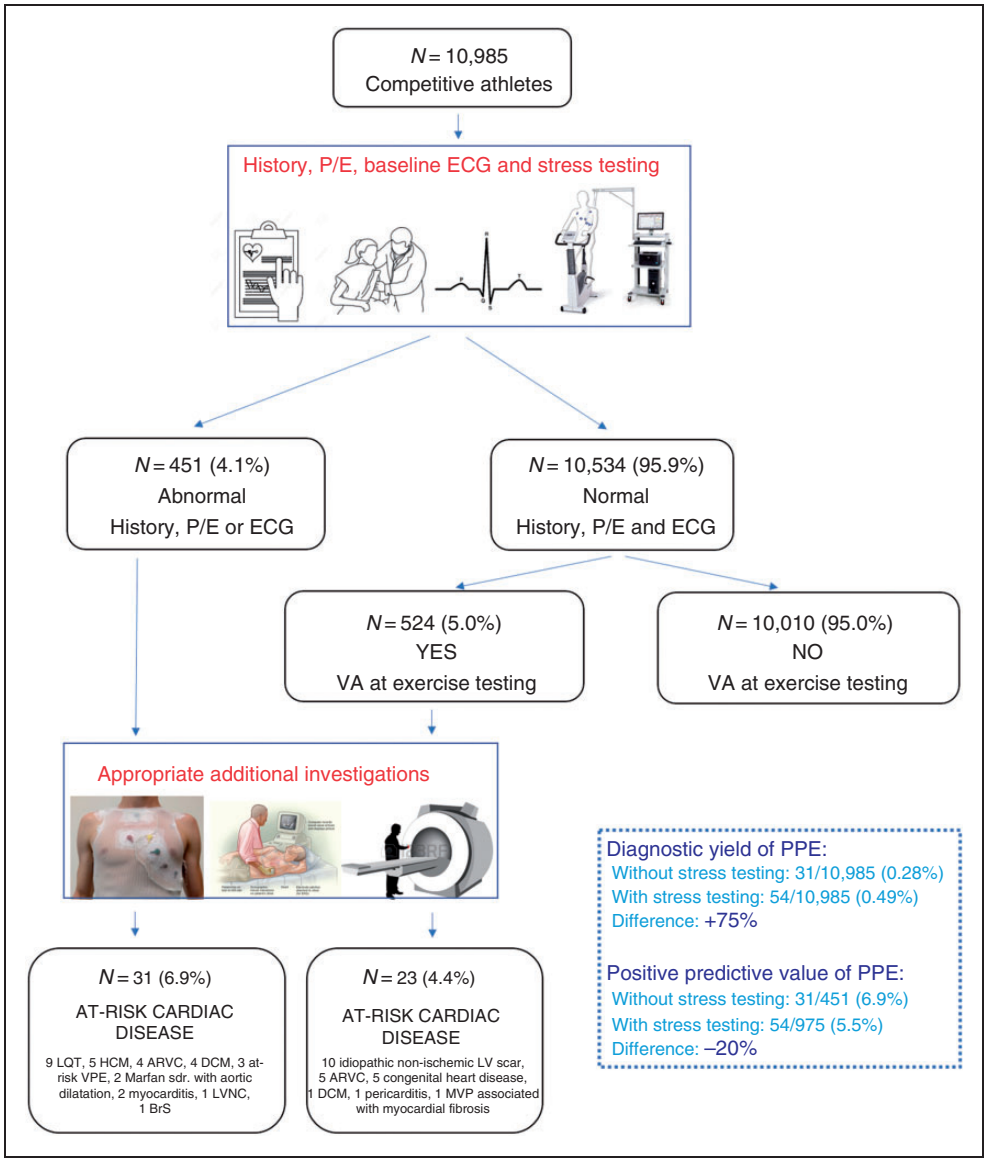

Figure 1. Schematic representation of the study protocol and result.
ARVC: arrhythmogenic cardiomyopathy; BrS: Brugada syndrome; DCM: dilated cardiomyopathy; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; LQT: long QT syndrome; LV: left ventricular; LVNC, LV non-compaction; MVP: mitral valve prolapse; P/E: physical examination; sdr: syndrome; VA: ventricular arrhythmia; VPE: ventricular pre-excitation.

prescribed additional investigations that resulted negative increased from 420 (3.8%) to 921 (8.4%) and the positive predictive value of PPE decreased by 20% (from 6.9% to 5.5%).

Management and follow-up

Athletes with a normal diagnostic work-up were considered eligible. Athletes with congenital heart diseases or ventricular pre-excitation were temporarily suspended from competitions and allowed to resume sports activity three months after uncomplicated correction or ablation. The other athletes with cardiac diseases at risk of SCD were disqualified from competitive sports activity, were given a clinical report that included tailored advice on leisure time exercise activities and prescribed pharmacological therapy as indicated (mostly beta-blockers). During a mean follow-up of 32 ± 21 months, the outcome of screened athletes (both with and without an underlying disease) was uneventful.

Discussion

The main study findings were that: 1. the addition of EST to history, physical examination and resting ECG increased the diagnostic yield of PPE for at-risk

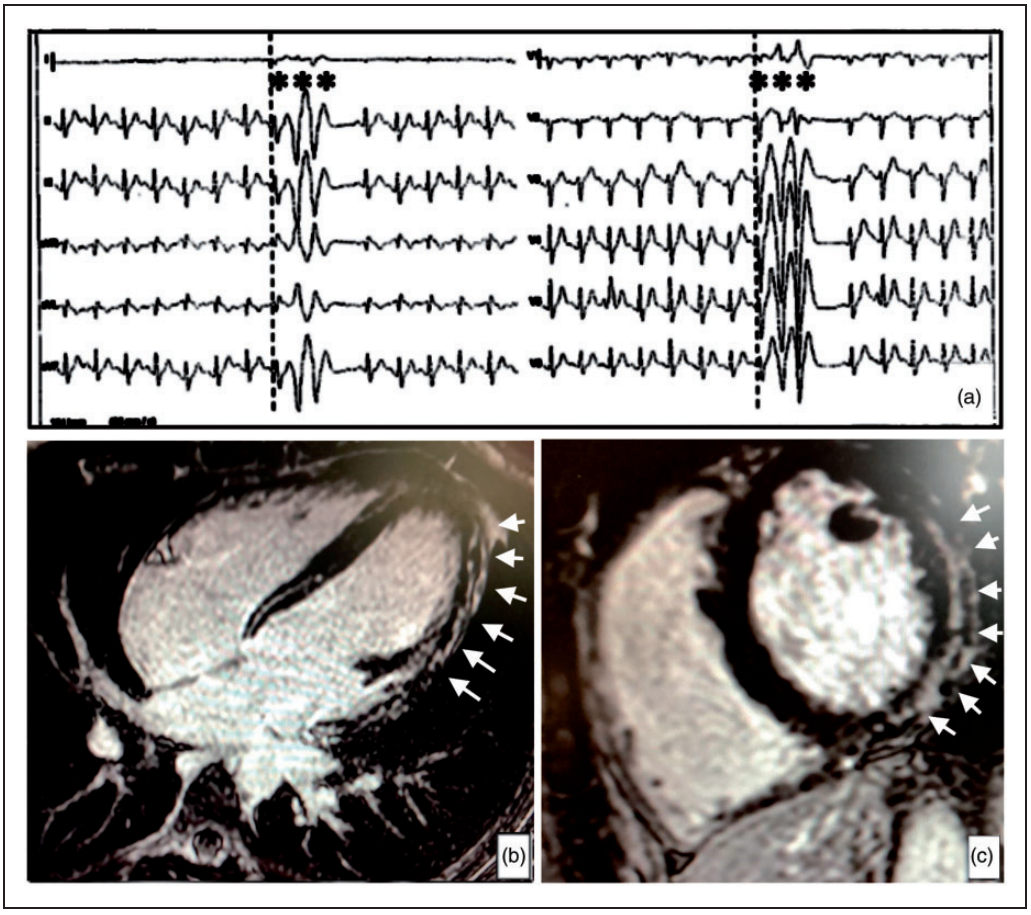

Figure 2. Representative case of a 17 year-old athlete with complex ventricular arrhythmias induced by stress testing.
The athlete had negative history, unremarkable physical examination and normal resting electrocardiogram. (a) During exercise-testing, complex ventricular arrhythmias with a right-bundle-branch-block/superior axis morphology were recorded at peak of exercise. Echocardiography was normal (not shown). On post-contrast cardiac magnetic resonance sequences, a subepicardial/midmyocardial stria of late gadolinium enhancement involving the left-ventricular wall was visible on: (b) short-axis view; (c) four-chambers view.

cardiovascular diseases from 0.28 to 0.49% but also decreased the positive predictive value from 6.9% to 5.5%; 2. the prevalence of athletes with normal history, physical examination and resting ECG who had EST-induced VA was 5.0% (524/10,534); 3. of these athletes with exercise-induced VA, 23 (4.4%) were diagnosed with a cardiac disease at risk of SCD that mostly consisted of an isolated non-ischaemic LV scar evidenced by CMR as subepicardial LGE on post-contrast sequences but undetectable by echocardiography; 4. predictors of such LV LGE included complexity and morphology of VA; and 5. no screened athlete, either eligible for competitive sports activity or not, according to the results of cardiovascular evaluation, experienced major arrhythmic events during follow-up.

Evolving role of EST for PPE screening

Exercise-testing is traditionally recommended for exclusion of myocardial ischaemia in master athletes with symptoms or risk factors for coronary artery disease or for evaluation of cardiorespiratory fitness.[13,14] However, EST may provide other clinical information including VA inducibility, which may be the sole manifestation of a cardiac disease at risk of SCD during sports activity. Although the prevalence and clinical significance of VA by EST have been assessed in the general population,[15,16] systematic studies on the diagnostic and prognostic impact of exercise-induced VA in the young athletic population are lacking.

In the present study, we evaluated the prevalence and clinical significance of exercise-induced VA in a large series of consecutive athletes undergoing cardiovascular evaluation before participation in sports, by reviewing findings of a constant-load EST that was systematically performed in addition to history, physical examination and resting ECG. All athletes with VA at EST underwent further evaluation consisting of 12-lead 24-hour ECG monitoring and echocardiography. CMR was reserved to a subset of athletes with more severe

Table 3. Characteristic of athletes with and without left-ventricular late gadolinium enhancement at cardiac magnetic resonance.

	Presence of LV LGE $n=16$	Absence of LV LGE $n=71$	p
Females	4 (25%)	15 (21%)	0.74
Age	17 [15–18]	16 [14–17]	0.08
Years of sports practice	5 [3–7]	9 [7–11]	0.10
Hours of training per week	6 [5–8]	5 [2–6]	0.80
Exercise testing			
Max/MaxT HR (%)	90 [86–92]	90 [86–93]	0.96
VA only at peak of exercise (3rd minute)	8 (50%)	19 (27%)	0.07
Couplets or NSVT	8 (50%)	10 (14%)	0.001
24-hour ambulatory ECG monitoring			
Max/MaxT HR (%)	90 [89–95]	94 [90–98]	0.92
PVBs count	234 [53–1241]	664 [47–3691]	0.03
PVBs >500/24 hours	6 (38%)	39 (55%)	0.21
Arrhythmia grading			0.25
Isolated PVBs only	2 (13%)	16 (25%)	
≥1 couplet	8 (50%)	21 (30%)	
≥1 NSVT	6 (38%)	32 (45%)	
Prevalent VA morphology*			
Infundibular/fascicular	2 (13%)	15 (21%)	0.73
LBBB and inter./sup. Axis	2 (13%)	22 (31%)	0.22
RBBB and QRS >130 ms or both LBBB and RBBB	12 (75%)	29 (41%)	0.02
VA during training session	11 (69%)	37 (56%)	0.36

Data are presented as *N* (%) or median [25%–75% percentiles].
HR: heart rate; LBBB: left-bundle-branch-block; LGE: late gadolinium enhancement; Max/MaxT HR: ratio between maximal heart rate recorded and theoretical maximal heart rate corrected for age (220 – age); NSVT: non-sustained ventricular tachycardia; PVBs: premature ventricular beats; RBBB: right-bundle-branch-block; VA: ventricular arrhythmia.
*Among athletes with at least 10 PVBs.

VA features or echocardiographic abnormalities. This protocol increased the diagnostic power of PPE by identifying 23 athletes with structural heart disease at risk of SCD among 524 with VA at EST but normal history, physical examination and resting ECG. At the same time, the proportion of athletes who were prescribed additional investigations that resulted negative (false positives) increased from 3.8% to 8.4%, leading to a decrease in the positive predictive value of PPE decreased by 20% (from 6.9% to 5.5%).

Underlying myocardial substrates

The most commonly identified myocardial substrate was the 'non-ischaemic myocardial fibrosis', in the form of isolated LGE involving the subepicardial/mid-myocardial layers of the LV wall. This myocardial lesion has been recently recognized as an arrhythmic substrate in athletes. Both previous investigations and the current study showed that the main clinical manifestation of non-ischaemic LV scar in athletes consist of exercise-induced, often repetitive, PVBs with a RBBB morphology. The resting ECG was usually normal suggesting it has a low sensitivity and is therefore unlikely to raise the suspicion for this condition at PPE. Echocardiography was also normal in most cases because of the segmental nature of the lesion confined to the subepicardial LV wall layers.[17–23]

Previous outcome studies provided evidence that the non-ischaemic LV scar may be associated with life-threatening VA and SCD.[17–20] In particular, we found in a previous investigation that, during a mean 3-year follow-up, 22% of athletes with non-ischaemic LV scars and VA experienced ICD shock, sustained ventricular tachycardia or SCD; in 5 of 6 cases the event occurred during exercise.[17] In the present study, none of the athletes who received a diagnosis of non-ischaemic LV scar experienced malignant events during follow-up. However, the two investigations differed in design (prospective versus retrospective) characteristics of the study population and clinical management (sports restriction).

Although isolated LV LGE with subepicardial/mid-myocardial distribution is traditionally interpreted as

the consequence of a previous myocarditis, there is increasing evidence that it may also reflect a left-dominant arrhythmogenic cardiomyopathy, characterised by fibrofatty myocardial replacement of the LV and VA with a RBBB morphology.[17,18,24] In this regard, we previously reported the case of a 39 year-old cyclist with CMR evidence of isolated non-ischaemic LV scar and complex VA at exercise testing.[17] The athlete, who was managed by a different sports medicine centre, was considered eligible to compete because the finding of LGE on CMR was interpreted as a sign of a healed (and benign) inflammatory process, although he did not have a clinical history of acute myocarditis. He died suddenly during a competitive race. Cascade clinical and molecular family screening showed that the non-ischaemic LV scar was the phenotypic expression of a familial desmosomal gene-related arrhythmogenic cardiomyopathy.

The recent European Society of Cardiology recommendations state that athletes with LV LGE and frequent or complex VA should refrain from competitive sports.[25] According to this recommendation, our athletes with non-ischaemic LGE were considered non-eligible to competitive sports activity because they had frequent, repetitive and/or exercise-worsened VA, which were the reason for deeper investigation including CMR.

Of the nine individuals who received a diagnosis of arrhythmogenic cardiomyopathy, five had a normal ECG and the disease was suspected only because of VA at EST. Although ECG abnormalities are reported in up to 85% of patients with overt arrhythmogenic cardiomyopathy, there is a correlation between the severity of the phenotype and the probability of exhibiting ECG changes.[26] Therefore, it is not surprising that young athletes at the beginning of the disease's natural history may still show an unremarkable ECG.

Work-up of exercise-induced VA

Our results demonstrated that VA at EST may be the only phenotypic manifestation of a pathological myocardial substrate in athletes with an otherwise normal history, physical examination and resting ECG. Because echocardiography may not be sensitive enough to exclude the presence of segmental myocardial fibrosis as a potential substrate of malignant VA, CMR should be considered in the diagnostic work-up of athletes with VA at EST.[23] However, because of the limited availability and high costs, CMR should be reserved to a subset of athletes with a high pre-test probability of abnormal findings. In this regard, our study showed that variables significantly associated with LV LGE were the presence of PVBs with RBBB/wide QRS at 12-lead 24-hour ambulatory ECG monitoring (either in isolation or associated with LBBB PVBs) and couplets/non-sustained ventricular tachycardia at EST.

Although recording of frequent PVBs at 24-hour ambulatory ECG monitoring was an indication to CMR according to our study protocol, we did not find any relationship between the number of PVBs and the presence of LGE at CMR. This may be explained by the different mechanism of VA: enhanced automaticity of a myocardial focus, unrelated to a cardiac disease, may result in a very high number of PVBs, while VA associated with pathological myocardial substrates are characteristically more often complex and adrenergic-dependent.[12]

Implications of adding stress testing to the PPE protocol

While cardiovascular evaluation before participation in sports is recommended by most medical societies and sports federations with the aim to identify asymptomatic athletes with heart diseases at risk of SCD, the best screening protocol remains a matter of debate. The American Heart Association suggests only history and physical examination whereas the European Society of Cardiology and the International Olympic Committee recommend to include a resting 12-lead ECG.[2,27,28] Although the ECG has a good sensitivity for the identification of leading causes of SCD including cardiomyopathies and channelopathies, it has limited value for detecting silent arrhythmogenic disorders such as segmental cardiomyopathies, acute myocarditis, non-ischaemic LV myocardial fibrosis and coronary artery disease, either congenital or acquired.[3]

Previous studies addressing the incremental role of echocardiography in addition to history, physical examination and resting ECG failed to demonstrate a significant impact of this imaging modality.[4–7] Instead, prior investigations suggested that EST could substantially increase the diagnostic yield of PPE.[29–31] Sofi et al. evaluated 30,065 individuals undergoing PPE and found that abnormalities at EST (including supraventricular arrhythmias or VA, ST-segment changes and intraventricular conduction disorders) allowed for the identification of a potentially fatal cardiac disorder in 56 participants with normal ECG (0.18%).[29] However, details on the protocol of EST and on the prevalence, work-up and underlying pathological substrates in individuals with VA during EST were lacking.

Our study confirmed and extended this previous observation by showing the unique ability of EST to unmask the exercise-induced ventricular electrical instability of concealed myocardial substrates. While physical examination and ECG allowed for the identification of overt cardiac abnormalities at risk of SCD in

0.28% of screened athletes, EST led to the diagnosis of concealed arrhythmogenic myocardial substrates in a further 0.21% of cases, thus increasing the sensitivity of PPE by 75%. On the other hand, it must be recognized that the addition of EST to history, physical examination and resting ECG reduced the positive predictive value of PPE and is expected to increase the costs.

Study limitations

The main limitation is that only a subset of athletes with EST-induced VA underwent CMR according to pre-specified indications based on arbitrary grading of the VA burden. This prevented the assessment of myocardial fibrosis in those athletes with VA who did not undergo CMR. Athletes with pathological myocardial substrates were disqualified from competitive sports activity according to Italian law and the national guidelines. Hence, we were unable to assess the outcome of athletes with heart diseases actively involved in competitive sport activities. According to the law, the EST was performed with a constant-load rather than with a conventional ramp protocol and was stopped after 3 minutes (if >85% of the maximal theoretical heart rate had been achieved) rather than being continued until volitional exhaustion, potentially limiting its sensitivity for detection of VA. Finally, the study mostly included adolescent non-professional athletes, hence, the results cannot be transferred to older individuals or elite athletes.

Conclusions

Our study has demonstrated that VA induced by EST may be a marker for underlying arrhythmogenic myocardial substrates in athletes with otherwise normal history, physical examination and resting ECG. In many cases, the concealed myocardial substrate consisted of a non-ischaemic LV scar that was missed by echocardiography and could only be revealed by CMR. On the other hand, in the majority of cases VA at EST were unrelated to an underlying heart disease and prompted second-line investigations that resulted in negative results.

In conclusion, the addition of exercise testing for the evaluation of VA inducibility to history, physical examination and ECG resulted in an increase of the diagnostic yield of PPE at the expense of an increase in false-positive results and costs.

Author contribution

AZ and TV contributed to the conception of the work, the analysis and interpretation of data, and manuscript drafting; PS and DC contributed to analysis and interpretation of data and critically revised the manuscript, MDL, AC and MPM contributed to the analysis and interpretation of data; VM, GS, SR, LM and CP contributed to data collection. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was supported by a research grant of the Italian Ministry of Health (RF-2014-00000394) and by the department of cardiac, thoracic and vascular sciences and public health of the University of Padova, Italy (BIRD-2016-162733).

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